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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,394	08/01/2001	Rosanne M. Crooke	ISPH-0589	4398

36441 7590 03/22/2004

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,394	CROOKE ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *February 24, 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-10,12,13,15 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10,12,13,15 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed January 7, 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed July 16, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. New claim 24 has been fully entered.

Information Disclosure Statement

4. The reference of Toyama et al submitted as part of the information disclosure statement filed May 6, 2003 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it is in a foreign language and a translation has not been provided. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1). While applicants have submitted a concise explanation of the relevance of Toyama, the translated reference must also be provided in order

to be considered. Additionally, applicants response implies that a translation of the abstract has been provided. No translation can be found in the file, and thus the abstract also has not been considered.

Response to Claim Rejections - 35 USC § 35 U.S.C. § 103(a)

Claims 4-10, and 12, 13, 15, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (U.S. Patent 5,968,749), or Chang et al. (U.S. Patent 5,484,727), in view of Baracchini et al. (U.S. Patent Number 5,801,154) and Taylor et al (Drug Disc. Today, 1999. 4(12) 562-567), and is repeated for the same reasons as set forth in the Office action mailed July 16, 2003.

Applicants traverse the instant rejection by arguing that Taylor must be removed as a reference, because Taylor "makes a misleading and unsupported allegation about the ease and straightforward manner of determining target sites on a gene that permit one to identify suitable antisense oligonucleotides of a high degree of inhibition for any gene." Applicants argue that the instantly disclosed techniques do not produce the expected and simple results as stated by Taylor. In support, applicants have provided a declaration under 37 CFR § 1.132. The declaration includes a statement from a representative of the assignee indicating her belief that it is never possible to predict reliably before the screen is performed, what gene will require screening of many oligos or just a few to find one capable of achieving significant inhibition. Applicants submit examples of two genes which were subjected to antisense-inhibition assays

using 80 different oligos per gene. Applicants report results whereby no oligo attained more than 50% inhibition against one gene, and 40% against the other.

At the outset, it is noted that the M.P.E.P. has no provisions which set forth considerations that must be made for an entire reference to be "removed from consideration" as requested. Applicants' objection to one statement in an article which has been peer-reviewed by other scientific experts in the field of antisense gene inhibition is not considered sufficient on its face to have all statements of Taylor et al. removed from consideration. Because Taylor et al. has been peer reviewed, and absent any evidence that the statements of Taylor were made under false pretences, Taylor et al. will not be removed from consideration, but will rather be considered in light of the evidence supplied by applicants. Applicants have provided data from two genes shows that they weren't able to screen 3-6 oligos to find one that inhibited 66-95%. Upon reading and considering applicants evidence and comments, it is maintained that the declaration is not considered convincing for multiple reasons.

First, applicants have not indicated whether these examples are considered to be representative of the results of such tests against any gene, or whether alternatively, they comprise the results from two genes for which applicants are having a difficult time finding oligos that inhibit to a specified level. Tables of antisense oligo inhibition assays from two randomly selected patents (the first two patents that resulted from a search for those with the term "antisense" in the claims) show that one could reasonably expect to screen a reasonable number of oligos and find at least a few capable of significant levels of target inhibition. For example, table 1 of U. S. Patent Number 6,001,992 (col. 27) contains tests results for 15 oligos, with 4 of the 15 exhibiting over 60% inhibition. Thus, the inventors of patent found 1 oligo

exhibiting 60% inhibition for every 3.6 screened, well within the range indicated by Taylor et al. A table from the other randomly selected different patent, U. S. Patent Number 6,312,900 (col. 21) returned a much higher number of hits, whereby 7 out of 10 oligos tested achieved inhibition of at least 60%. This is 1 oligo for every 1.4 tested that achieve said level of inhibition. Thus, a strong case can thus be made that applicants' submitted data may not be representative of every instance of antisense oligonucleotide mediated gene inhibition. These citations do not constitute a new grounds of rejection, but are merely provided to rebut applicants arguments and declaration.

Second, applicants have not established whether the assays provided in the declaration fall within the conditions taught by Taylor et al. For example, Taylor et al. teaches that in order to achieve this inhibition, high affinity chimeras must be used. While applicants have certainly used chimeric oligos comprising DNA and RNA, these do not appear to be high affinity chimeras, that is those that contain modifications designed to increase hybridization affinity. Applicants have not indicated either way what their conditions are relative to the teachings of Taylor et al., and thus it is not clear how such evidence is related to Taylor, let alone defeats Taylor.

Third, even if applicants were to clearly establish that Taylor is wrong, and that one of ordinary skill would need to screen more than 3-6 oligos using modern bioinformatics and high affinity chimeras to find an oligo that inhibits at least 66%, an assertion that is not adopted by the examiner, any alleged lack of enablement in Taylor must address is how many more oligos would one of ordinary skill have to screen, and ultimately whether this increased amount of experimentation is undue. It is clearly established case law that the amount of experimentation is

not undue if one is reasonably assured of predictably reaching the claimed result, irrespective of the amount of work involved. While applicants recite that occasionally, an upper limit of more than 70 oligos need to be screened for inhibition, it is maintained that this level of experimentation is not undue. One of ordinary skill in the art practicing the methods known in the art and set forth, for example by Baracchini (of record), would be reasonably assured of finding among the 70 at least one oligo that inhibits its respective target to the claimed degree of 12 or 30 %, and probably much more in view of the results from the randomly found antisense patents cited above. In this case, applicants do not even allege that such unpredictability exists in the art, but just merely assert that it would probably take screening more than 3-6 oligos. If applicants are suggesting that the state of the art is so unpredictable that one of ordinary skill might try every conceivable oligo directed against a specific target *in vitro* and never achieve any inhibition, which they have not done, applicants are invited to clearly state such an assertion on the record, and provide evidence in support of such an assertion. In the absence of this, it is maintained that Taylor, and the state of the art of using antisense *in vitro* in general is considered to be enabled.

Applicants further argue that while Chang does disclose using antisense to target ACAT, Chang does not disclose methods of using such antisense compounds to inhibit endogenous ACAT expression in cells or tissues, as instantly claimed. Applicants further argue that the disclosure of Chang is extremely generic and can be found in any reference or review article discussing antisense technology. Applicants assert that Chang provides only a suggestion for using a generic antisense compound, for which no description is provided.

These arguments are not considered to overcome this reference, because as an obviousness rejection, this rejection is based on a combination of references, and applicants arguments merely cite those elements which were not relied upon in Chang, but are nevertheless taught by the other references. It is acknowledged that Chang provides express motivation, but does not provide explicit detailed instructions one would need to practice to carry out the invention. These are provided by Taylor, but more so by Baracchini et al. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Chang et al. was relied upon for teaching the ACAT transcript, and also for motivation to inhibit the ACAT target, because Chang et al. expressly teach its inhibition via antisense mediated targeting. Although applicants argue that the ACAT target of Chang is not endogenous, this limitation is not considered relevant, because whether the ACAT is endogenous or is introduced does not change any quality of the compound actually being claimed, that is, the antisense molecule, so long as the ACAT sequence is the same.

Applicants' objection to Baracchini is based on the fact that Baracchini does not mention the ACAT molecule. Applicants assert that since Baracchini et al. adds nothing to Chang, and that it does no more or less than reiterate the generic antisense teachings.

The argument that Baracchini does not provide anything more than a generic teaching of how to achieve antisense inhibition is without any merit. When one reads Baracchini, it becomes apparent that Baracchini teaches to minute detail the precise steps and reagents necessary to achieve antisense mediated gene inhibition. Furthermore, Taylor et al. teaches that such methods

are expected to apply to any gene, so long as the sequence is known. Regarding Baracchini, this reference has exemplified the synthesis of oligonucleotides, including specific molecules to use identified by scientific nomenclature along with their manufacturers, and their locations. Baracchini discloses step by step protocols for the synthesis of standard oligoribonucleotides and further details how to make such oligos in their modified form, to a level of detail that includes concentrations of starting reagents, solvents, heating and incubation times, assays to assess target cleavage including all of the above information, along with selection of cell lines and whole animal models. What's missing from Baracchini is a suggestion to target the ACAT transcript, which is provided by Chang. The claims thus stand rejected.

Claim Rejections - 35 USC § 112

Claims 4-10, 12, 13, 15, and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to compounds 8 to 50 nucleotides in length that hybridize with nucleobases 14 to 1741 of SEQ ID NO: 3, wherein said oligo demonstrates at least 12% inhibition of the expression of a nucleic acid molecule encoding acyl coenzymeA cholesterol acyltransferase-1 (ACAT).

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.

Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The language of claim 4 broadly embraces any sequence that hybridizes to SEQ ID NO: 3 (an ACAT isoform) and inhibits any ACAT. The claim is not limited to the inhibition of SEQ ID NO: 3, but rather to any oligo that inhibits any ACAT so long as it also hybridizes to nucleobases 14-1741 of SEQ ID NO: 3. Applicants are not considered to be in possession of the genus of oligos that hybridize to any ACAT, because "hybridization" is considered to be an extremely broad functional term. Hybridization is dependent upon a number of different factors that include the percent identity that the oligo has for its target, the temperature of the solution

that hybridization is to take place in, the salinity of said solutions, GC content, among other things. As stated in the specification, "It is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." Thus, because of the amount of substitution allowed for by such language, claim 1 is considered to be directed to the genus of oligos that not only hybridize to SEQ ID NO: 3, but also to explicitly claim oligos directed to any ACAT target regardless of species, allele, homolog or variant, because of the claim language in claim 1 specifying oligos capable of "inhibition of a nucleic acid molecule encoding ...ACAT in a cell..."

Accordingly, the specification should include a representative sample of oligos that hybridize to any ACAT from a group comprising any species that express ACAT, including any isoforms, variants and alleles present within these species, and also including any oligo that hybridizes to transcripts that are within reasonable similarity that retain ACAT function. As set forth above, this can be achieved by disclosing a representative sample of the complete or partial structure of such oligos, or physical and/or chemical, structure/function correlation, or any combination thereof in order to be considered to be in possession of the claimed genus.

However, applicants have only disclosed oligos that possess 100% identity to SEQ ID NO: 3. No oligos have been disclosed with less than 100% identity, and no oligos have been disclosed as hybridizing to any other ACAT transcripts, let alone hybridize to any homologs, alleles, variants, or fragments from any other species. Accordingly, a person of skill in the art would not view oligos that hybridize with 100% identity to SEQ ID NO: 3 as adequately describing a representative sample of the broad genus of isoforms, alleles, and variants encoding ACAT in any species as claimed, and would thus conclude that applicant was not in possession

of the invention as stated. The specification thus does not provide adequate written description for sequences that are antisense to any polynucleotide encoding ACAT that are heretofore undescribed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James Douglas Schultz, PhD

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1635